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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,136	08/28/2003	Sandor Sipka	22740-2	8175

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	
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05/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,136	SIPKA ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-18 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *6-9,11,12,14-16,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 10, 13, 17-18 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 02/22/2010, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649

2. Claims 1-3 and 5-18 and 20-25 are pending.

3. Claims 6-9, 11-12, 14-16 and 20-21 stand withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a nonelected species.

4. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are currently under examination as they read on a process for inhibiting allergic disease in humans by aerosol administration.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cochran et al. (PTO-892 mailed on 01/29/2008; Reference U) in view of Previte et al. (PTO-892 mailed on 05/16/2007; Reference W) and Baldridge et al. (PTO-892; Reference U).

Cochran et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (2-3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (E.coli LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during nasal aspiration) during

maturation of the mammal (at 2-3 weeks) (In particular, abstract, page 268, right column, whole document).

Cochran et al. also teaches that "recent studies raised the intriguing hypothesis that exposure to LPS may interact with the immune system in early life and produce a protective environment against the development of asthma and atopy. Despite the potential importance of this phenomenon in the pathogenesis of childhood asthma, only recently have animal models been used to study the interactions between endotoxin and allergic responses as a function of age" and "patients become symptomatic in their first 5 years of life" (In particular, page 268, left column).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24 ; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retainining antigenticity (maintaining its Th1 stimulatory effect) and pyrogenicity (In particular, abstract, whole document).

Baldridge et al. teaches the weekly intranasal vaccination of mice with the adjuvant monophosphoryl lipid A (MPL), which is derived from lipopoysaccharide and has retained immunostimulatory properties and decreased toxicity, resulting in increased Th1 responses (In particular, abstract, 'Vaccinations' section on page 2417, whole document).

The functional limitations of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the term "living environment" and "living space" Therefore, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and

frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It is also noted that the recitation of wherein the administration is on a daily basis reads on a single administration without a further recitation regarding the number of days the administration occurs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Cochran et al in humans of 1 month to 2 years of age and during the maturing life cycle of the mammal. Cochran et al. suggests performing the process for decreasing development of allergic asthma in young children under 5 years of age implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Cochran et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

It would have been obvious to administer the detoxified LPS at least weekly because Baldridge et al. teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th1 response.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 02/22/2010 as applied to the instant rejection have been fully considered, but are not found persuasive.

Applicant argues:

> "To establish *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Summarily, Appellants submit that Cochran fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Cochran used LPS rather than IR-LPS in his experiments. Second, Cochran teaches only a one-time exposure to an immature mammal, while Appellants teach repeated exposure over a critical maturation period. Third, Cochran teaches application of LPS directly to the subject (via intranasal instillation), while Appellants teach indirect exposure by application of IR-LPS to the living environment of the mammal. All of these elements are disclosed by Appellants as critical to the efficacy of the inventive method, yet the Examiner dismisses the absence of the latter two, and applies Previte - a reference that teaches only direct administration of IR-LPS to adult mammals to test for a decrease in toxicity, reporting death of nearly a third of the subjects 6 days post-administration (see, e.g., Fig. 3), and "extensive inactivation of antigenic components with increasing radiation dose" (page 1611, second column, line 11-14).
>
> Appellants note that if it were true that the disclosure of Previte would guide an ordinary practitioner to the use of IR-LPS in the methods of Cochran (as the Examiner asserts), then surely Cochran himself would have employed IR-LPS since Previte's findings were published some 35 years prior to Cochran. However, even if the combination of references were proper, which Appellants contend it is not, Previte simply does not overcome the deficiencies of Cochran. At least two elements of the instant

invention remain wholly unaddressed by the combined references: the passive administration of IR-LPS to the living environment of the mammal, and the repeated administration of IR-LPS over a period of maturation of the mammal ("at least weekly" in independent claims 1 and 25 and "during maturation of the mammal" in independent claim 22).

All claim limitations must be considered in an obviousness rejection. 35 U.S.C. § 103 provides that:

A patent may not be obtained.., if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a **whole** would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. (Emphasis added). Since Cochran and Previte together completely fail to address administration of IR-LPS to the environment of the mammal, through repeated doses during the maturation period of the mammal, Appellants assert the combined references fail to render obvious the subject matter as a whole. Absent any teaching or suggestion of the missing claim elements, Appellants submit the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103.

Moreover, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000). Appellants note that not only does Previte fail to disclose or suggest the missing elements of administration across a maturation period and indirect exposure to the environment as the form of administration, Previte in fact discloses the retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner away from direct administration to an immature subject. Indeed, Previte reports a death rate of 3/10 adult subjects 6 days post-administration. And yet, the Examiner expressly states the motivation for using Previte's IR-LPS in the method of Cochran is specifically because a practitioner would conclude, based on the teachings of Previte, that the method would be "safe" for children and infants. The Examiner's assertion that the motivation to combine the references is "because it would be safe for children" is untenable, given the reported death rate associated with Previte's findings. Appellants contend that a positive death rate of 3/10 adult subjects predictably due to the treatment, as disclosed by Previte for IR-LPS levels within the scope of the instant invention, would be universally understood as unacceptable. Rather, a person of ordinary skill in the art seeking methods to prophylactically decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocol of Cochran, as Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate among the subjects.

The Examiner contends that, because IR-LPS is the active, therefore all effects on the subjects are inherent. In taking this position, though, the Examiner fails to consider the distinguishing impact of the route and manner of administration. The Examiner cannot fairly conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Indeed, Appellants note that Previte supports this proposition, since Previte discloses a single dose of IR-LPS administered directly to the subject, which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on repeated passive dosing during the maturation period of the mammal by misting the environment without toxic effect. Clearly, given these disparate results, route and manner of administration are distinguishing factors that lead to different toxicity and antigenicity outcomes.

In summary, Appellants assert the combination of Cochran and Previte fails to teach or suggest at least two important claim limitations -- administration of IR-LPS repeatedly, during the maturation of the mammal, and indirect administration via treatment of the living environment of the mammal. Moreover, motivation to combine the references is absent, given Previte's unacceptably high reported death rate of 3/10 adult subjects. Appellants submit a prima facie case for obviousness under 35 U.S.C. § 103 has not been established by the Examiner."

"To render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the art to make and use the later invention. The prior art must place the claimed invention in the possession of the public. Beckman Instruments, Inc. v. LKB Produktor LB, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Appellants submit the combination of Cochran and Previte does not enable the instant invention, since all claim elements are not taught or suggested by the references and one of ordinary skill in the art could not derive the claimed methods from the cited references without undue experimentation. Even if the combination of Cochran and Previte were proper (which Appellants contend it is not, in detail above), the combination itself still fails to enable the instant inventive methods. Combining the IR-LPS of Previte with the protocol of Cochran still enables, at best, nothing more than a single dose of IR-LPS, administered invasively to a mammal via intra-nasal instillation of a solution comprising IR-LPS. Appellants note that the ultimate findings of Cochran teach only that a "single airway exposure to LPS in young mice leads to airway hyperresponsiveness." (Cochran, p. 272, col. 1, lines 6-8). Appellants' methods, however, require administration of IR-LPS to the living environment of the mammal through repeated treatments during the maturation of the mammal. Deriving the instant methods from a reading of Cochran and Previte requires altering both mode and frequency of administration, either one of which would require undue experimentation on the part of the ordinary skilled artisan to achieve. That is, a practitioner would need to first conceive of the idea of administering IR-LPS to the living environment of the mammal, rather than direct intra-nasal instillation (Cochran) or injection (Previte) of the mammal itself, without any guidance or direction whatsoever in the cited references. Then, the practitioner would need to experiment with different dosing regimens - varying from the single doses described in both Cochran and Previte - in order to determine the present inventive method of decreasing development of allergic asthma in the mammal. Given the unpredictability in the art, the absence of direction in Cochran and Previte, and the quantity of experimentation needed relative to the references, Appellants contend such a leap would necessarily require undue experimentation on the part of the ordinary skilled artisan. Since Cochran and Previte together fail to place the present invention in the possession of the public, Appellants submit the instant inventive methods are not enabled by Cochran and Previte."

"Even if a prima facie case of obviousness under § 103 were established, Appellants' secondary evidence of nonobviousness rebuts the case. The Declaration of Dr. Sfindor Sipka, M.D., Ph.D., executed February 23, 2009, filed March 2, 2009 ("The March 2009 Declaration"), included herewith in the Evidence Appendix, demonstrates unexpected results and must be afforded due consideration. i) The evidence should be afforded substantial weight because a nexus exists between the claimed invention and the evidence of unexpected results provided in the March 2009 Declaration. In the March 2009 Declaration, Dr. Sipka described experimental protocols and results relating to comparing the in vivo immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (as a mist sprayed into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6). The Examiner has asserted that the Declaration does not provide evidence of an unpredicted differential impact of IR-LPS over LPS. The Examiner merely dismissed the data set forth in the Declaration as "neither surprising nor ... commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly." To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed. The examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.,* 776 F.2d 281,305, 227 USPQ 657, 673-674 (Fed. Cir. 1985), *cert. denied,* 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,* 851 F.2d 1387, 7 U.S.P.Q.2d 1222 (Fed. Cir.), *cert. denied,* 488 U.S. 956 (1988).

> Appellants submit the March 2009 Declaration is most certainly relevant to the instantly claimed methods. The experimental method reported in the March 2009 Declaration aligns with the present claims, including (1) exposing immature mammals (6 week mice at beginning of treatment) to either IR-LPS or LPS (2) on an at least weekly basis (daily for eight weeks, during the maturation period of the mammal) (3) to the living environment of the mammal (misting the cages). In order to assess the effects on development of allergic disease, animals were then sensitized with ragweed allergen and later challenged with the allergen. Macrophage and neutrophil counts were determined for bronchial lavage samples (BAL), as well as cytokine concentrations for TNF-~ (a TH 1 cytokine), IL-4, and IL-5 (a Th 2 cytokine). (See March 2009 Declaration, page 2, paragraph 4). The effect on allergic disease development was evaluated by assessing these indicators of allergic disease -- macrophage and neutrophil numbers, as well as *in vivo* immunomodulatory effects on cytokines, particularly the TH 1 cytokine, TNF-α
>
> Clearly, a nexus exists between the claimed invention, which provides methods for decreasing allergic asthma, and the data, which demonstrate the comparative unexpected superiority of IR-LPS in protecting against allergic disease, as evidenced by analysis of macrophage and neutrophil numbers as well as TNF-α levels. That is, a legally and factually sufficient connection between the claimed invention and the objective evidence of nonobviousness is present, such that the evidence should be considered in the determination of nonobviousness. Given the nexus between Dr. Sipka's data and the instant claimed invention, Appellants submit the Examiner erred in failing to consider and afford proper weight to the factual evidence provided by Dr. Sipka in the March 2009 Declaration.
>
> The surprisingly superior effect of IR-LPS over native LPS provides evidence of unexpected results that rebuts any prima facie case of obviousness. Appellants submit the results reported in the March 2009 Declaration provide evidence of the surprising superiority of IR-LPS compared to native LPS, with respect to stimulating the TH 1 arm of the immune system and protecting against hyper-immune response to an allergen. According to Dr. Sipka, the results illustrate "a striking difference between the in vivo immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers," (March 2009 Declaration, page 3, paragraph 6). Further, TNF-ct levels were increased significantly by 3.56 fold compared to controls for the IR-LPS, as compared with 1.66 fold for native LPS (see March 2009 Declaration, page 3, paragraph 6). Dr. Sipka specifically stated the results indicate a "surprisingly superior effect of IR-LPS over LPS in protecting against the development of hyper-immune response to an allergen neither taught nor suggested by any of the prior art" cited by the Examiner or known to him (March 2009 Declaration, page 4, paragraph 7). Neither Cochran nor Previte teach or suggest the superior effects of IR-LPS compared to native LPS in protecting against the development of allergic disease. Accordingly, Appellants submit the March 2009 Declaration provided by Dr. Sipka constitutes secondary evidence of nonobviousness rebutting any prima facie case of obviousness, since it clearly demonstrates that, specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results in decreasing allergic response, relative to native LPS.
>
> For the reasons set forth above, Appellants respectfully request that the Board reverse the final rejection of claims 1-3, 5, 10, 17-18, and 22-25 as being obvious under 35 U.S.C. § 103 over Cochran in view of Previte."

It is the Examiner's position that Applicant is arguing limitations that are not present in the claims when they argue that "Applicants teach a continual exposure over a critical developmental period" and that "Applicants teach indirect exposure by application of IR-LPS to the environment." The claims are not limited to methods comprising these two limited assertions. "At least weekly administration during maturation of the mammal" is not equivalent

to "continual exposure over a critical developmental period" and "to a living environment of the mammal" is not equivalent to "indirect exposure by application of IR-LPS to the environment" as defined by the specification. The claims are given their broadest reasonable interpretation, given the definitions and disclosure in the specification and intranasal administration is encompassed by the term "to a living environment of the animal" contrary to Applicant's assertion.

Applicant's argument that if the combination of Cochran and Previte was obvious, then Cochran himself would have employed IR-LPS since Previte was published 35 years prior to Cochran. is not persuasive. The Examiner has provided sound reasoning for combining the teachings of the references. The fact that the authors of the reference did not combine the teachings is not relevant to the instant rejection nor is it a persuasive argument to overcome an obviousness rejection.

It is the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. for purposes of the instant rejection what is or is not an "acceptable" degree of toxicity is not for Applicant to decide, nor is it a matter of what standards are presently medically acceptable for humans in the United States. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The reference teaches that toxicity is decreased and that

teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Cochran et al. references.

Applicants assert evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. However, such evidence has not been brought forth in the instant application that is commensurate in scope with the claims, including the Declaration by Sandor Sipka filed on 03/02/2009. The results set forth in the declaration are neither surprising nor are they commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly. Applicants are encouraged to submit additional data that is commensurate in scope with the claimed invention to demonstrate surprising or unexpected results. The Examiner is not arguing that the data in the Declaration is not relevant. The Examiner argues that the data is not surprising or commensurate in scope with the claimed invention. The irradiated LPS is not surprisingly better than non-irradiated LPS, which is what Applicant would need to establish to prove that the results were unexpected. Further, the results do not demonstrate decreased development of allergic asthma in a neonatal or immature mammal by exposure with irradiation-detoxified LPS to a living environment.

Cochran discloses a resulting airway hyperresponsiveness that results in a decrease in airway response to an allergen, upon administration of LPS to developing mice. The reference need not teach prevention or permanent efficacious treatment for airway hyperresponsiveness in order to be used as a reference. The lack of complete prevention of hyperresponsiveness does not "teach away" from the instant invention.

7. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al. (PTO-892 mailed on 01/29/2008, Reference V) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) and Baldridge et al. (PTO-892; Reference U).

Khan et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during intratracheal aspiration) during maturation of the mammal (at 3 weeks) (In particular, abstract).

Khan et al. teaches "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retainining antigenticity (maintaining its Th1 stimulatory effect) and pyrogenicity (In particular, abstract, whole document).

Baldridge et al. teaches the weekly intranasal vaccination of mice with the adjuvant monophosphoryl lipid A (MPL), which is derived from lipopoysaccharide and has retained immunostimulatory properties and decreased toxicity, resulting in increased Th1 responses (In particular, abstract, 'Vaccinations' section on page 2417, whole document).

The functional limitations of The recitation of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed

subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the term "living environment" and "living space" Therefore, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It is also noted that the recitation of wherein the administration is on a daily basis reads on a single administration without a further recitation regarding the number of days the administration occurs.

Khan et al. teaches "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract), it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Khan et al in humans of 1 month to 2 years of age

and during maturation. Khan et al. suggests performing the process for decreasing development of allergic asthma in young post-natal children implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

It would have been obvious to administer the detoxified LPS at least weekly because Baldridge et al. teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th1 response.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 02/22/2010 have been fully considered, but are not found persuasive.

Applicant argues:

To establish *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Summarily, Appellants submit that Khan fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Khan used LPS rather than IR- LPS in his experiments. Second, Khan teaches only a one-time exposure to an immature mammal, while Appellants teach repeated exposure over the maturation period. Third, Khan teaches application of LPS directly to the subject (via intratracheal administration), while Appellants teach indirect exposure by application of IR-LPS to the living environment of the mammal. All of these elements are disclosed by Appellants as critical to the efficacy of the inventive method, yet the Examiner again dismisses the absence of the latter two, and applies Previte - a reference that teaches only direct administration of IR-LPS to adult mammals to test for a decrease in toxicity, reporting death of nearly a third of the subjects 6 days post- administration (see, e.g., Fig. 3), and "extensive inactivation of antigenic components with increasing radiation dose" (page 1611, second column, line 11-14).

Even if the combination of references were proper, which Appellants contend it is not, Previte simply does not overcome the deficiencies of Khan. At least two elements of the instant invention remain wholly unaddressed by the combined references: the passive administration of IR-LPS to the living environment of the mammal, and the repeated administration of IR-LPS over a period of maturation of the mammal ("at least weekly" in independent claims 1 and 25 and "during maturation of the mammal" in independent claim 22).

All claim limitations must be considered in an obviousness rejection. 35 U.S.C. § 103 provides that:

A patent may not be obtained.., if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. (Emphasis added). Since Khan and Previte together completely fail to address administration of IR-LPS to the environment of the mammal, through repeated doses during the maturation period of the mammal, Appellants assert the combined references fail to render obvious the subject matter as a whole. Absent any teaching or suggestion of the missing claim elements, Appellants submit the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103.

Further, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). Appellants submit that Khan explicitly teaches away from the use of LPS in reducing subsequent allergic responses, and since Khan states that "airway exposure to LPS produces transient AHR (airway hyperresponsiveness) and inflammation in developing mice and does not appear to influence functional and immune responses induced by subsequent allergen sensitization" (Khan, last paragraph, emphasis added). The Examiner contends that Khan "is being relied upon for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma." However, the Examiner's application of Khan completely disregards the ultimate conclusion of Khan, which is that LPS produces only transient airway hyperresponsiveness and does not appear to influence later functional and immune responses to allergic challenge. Indeed, Khan expressly teaches that LPS does not appear to influence the *very responses* sought to be elicited by the present invention. Accordingly, Appellants submit Khan in fact teaches away from the present inventive methods.

Moreover, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by

the inventor. *See Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000). Appellants note that not only does Previte fail to disclose or suggest the missing elements of administration across a maturation period and indirect exposure to the environment as the form of administration, Previte in fact discloses the retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner awa2~ from direct administration to an immature subject. Indeed, Previte reports a death rate of 3/10 adult subjects 6 days post-administration. And yet, the Examiner expressly states the motivation for using Previte's IR-LPS in the method of Khan is specifically because a practitioner would conclude, based on the teachings of Previte, that the method would be "safe" for children and infants. The Examiner's assertion that the motivation to combine the references is "because it would be safe for children" is untenable, given the reported death rate associated with Previte's findings. Appellants contend that a positive death rate of 3/10 adult subjects predictably due to the treatment, as disclosed by Previte for IR-LPS levels within the scope of the instant invention, would be universally understood as unacceptable. Rather, a person of ordinary skill in the art seeking methods to prophylactically decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocol of Khan, as Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate among the subjects.

The Examiner contends that, because IR-LPS is the active, therefore all effects on the subjects are inherent. In taking this position, though, the Examiner fails to consider the distinguishing impact of the route and manner of administration. The Examiner cannot fairly conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Indeed, Appellants note that Previte supports this proposition, since Previte discloses a single dose of IR-LPS administered directly to the subject, which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on repeated passive dosing during the maturation period of the mammal by misting the environment without toxic effect. Clearly, given these disparate results, route and manner of administration are distinguishing factors that lead to different toxicity and antigenicity outcomes.

In summary, Appellants assert the combination of Khan and Previte fails to teach or suggest at least two important claim limitations - administration of IR-LPS repeatedly, during the maturation of the mammal, and indirect administration via treatment of the living environment of the mammal. Moreover, Khan in fact teaches away from the present inventive methods, and motivation to combine the references is absent, given Previte's unacceptably high reported death rate of 3/10 adult subjects. Appellants submit a prima facie case for obviousness under 35 U.S.C. § 103 has not been established by the Examiner."

To render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the art to make and use the later invention. The prior art must place the claimed invention in the possession of the public. Beckman Instruments', Inc. v. LKB *Produktor LB,* 892 F.2d 1547, 1551 (Fed. Cir. 1989). Appellants submit the combination of Khan and Previte does not enable the instant invention, since all claim elements are not taught or suggested by the references and one of ordinary skill in the art could not derive the claimed methods from the cited references without undue experimentation.

Even if the combination of Khan and Previte were proper (which Appellants contend it is not, in detail above), the combination itself still fails to enable the instant inventive methods. Combining the IR-LPS of Previte with the protocol of Khan still enables, at best, nothing more than a single dose of IR-LPS, administered invasively to a mammal via intratracheal administration of a solution comprising IR-LPS. Appellants note that the ultimate findings of Khan teach only that a "airway exposure to LPS produces transient AHR (airway hyperresponsiveness) and inflammation in developing mice" and, importantly, "does not appear to influence functional and immune responses induced by subsequent allergen sensitization (Khan, last paragraph, emphasis added). Appellants' methods, however, require administration of IR-LPS to the living environment of the mammal through repeated treatments during the maturation of the mammal in order to decrease development of allergic asthma.

Deriving the instant methods from a reading of Khan and Previte requires altering both mode and frequency of administration, either one of which would require undue experimentation on the part of the ordinary skilled artisan to achieve, as well as conjuring an expectation of success in spite of Khan's teaching away from any such expectation. A practitioner would need to conceive of the idea of administering IR-LPS to the living environment of the mammal, rather than direct intratracheal instillation (Khan) or injection (Previte) of the mammal itself, without any guidance or direction whatsoever in the cited references. Then, the practitioner would need to experiment with different dosing regimens - varying from the single doses described in both

Khan and Previte - in order to determine the present inventive method of decreasing development of allergic asthma in the mammal. Given the unpredictability in the art, the absence of direction in Khan and Previte, Khan's express teaching away, and the quantity of experimentation needed relative to the references, Appellants contend such a leap would necessarily require undue experimentation on the part of the ordinary skilled artisan. Since Khan and Previte together fail to place the present invention in the possession of the public, Appellants submit the instant inventive methods are not enabled by Khan and Previte."

"Even if a prima facie case of obviousness under § 103 were established, Appellants' secondary evidence of nonobviousness rebuts the case. The Declaration of Dr. Sfindor Sipka, M.D., Ph.D., executed February 23, 2009, filed March 2, 2009 ("The March 2009 Declaration"), included herewith in the Evidence Appendix, demonstrates unexpected results and must be afforded due consideration. i) The evidence should be afforded substantial weight because a nexus exists between the claimed invention and the evidence of unexpected results provided in the March 2009 Declaration. In the March 2009 Declaration, Dr. Sipka described experimental protocols and results relating to comparing the in vivo immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (as a mist sprayed into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6).

The Examiner has asserted that the Declaration does not provide evidence of an unpredicted differential impact of IR-LPS over LPS. The Examiner merely dismissed the data set forth in the Declaration as "neither surprising nor ... commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly."

To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed. The examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281,305, 227 USPQ 657, 673-674 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 7 U.S.P.Q.2d 1222 (Fed. Cir.), *cert. denied*, 488 U.S. 956 (1988).

Appellants submit the March 2009 Declaration is most certainly relevant to the instantly claimed methods. The experimental method reported in the March 2009 Declaration aligns with the present claims, including (1) exposing immature mammals (6 week mice at beginning of treatment) to either IR-LPS or LPS (2) on an at least weekly basis (daily for eight weeks, during the maturation period of the mammal) (3) to the living environment of the mammal (misting the cages). In order to assess the effects on development of allergic disease, animals were then sensitized with ragweed allergen and later challenged with the allergen. Macrophage and neutrophil counts were determined for bronchial lavage samples (BAL), as well as cytokine concentrations for TNF-a (a TH 1 cytokine), IL-4, and IL-5 (a Th 2 cytokine). (See March 2009 Declaration, page 2, paragraph 4). The effect on allergic disease development was evaluated by assessing

these indicators of allergic disease -- macrophage and neutrophil numbers, as well as in vivo immunomodulatory effects on cytokines, particularly the TH 1 cytokine, TNF-a. Clearly, a nexus exists between the claimed invention, which provides methods for decreasing allergic asthma, and the data, which demonstrate the comparative unexpected superiority of IR-LPS in protecting against allergic disease, as evidenced by analysis of macrophage and neutrophil numbers as well as TNF-a levels. That is, a legally and factually sufficient connection between the claimed invention and the objective evidence of nonobviousness is present, such that the evidence should be considered in the determination of nonobviousness. Given the nexus between Dr. Sipka's data and the instant claimed invention, Appellants submit the Examiner erred in failing to consider and afford proper weight to the factual evidence provided by Dr. Sipka in the March 2009 Declaration.
ii)The surprisingly superior effect of IR-LPS over native LPS provides evidence of unexpected results that rebuts any prima facie case of obviousness. Appellants submit the results reported in the March 2009 Declaration provide evidence of the surprising superiority of IR-LPS compared to native LPS, with respect to stimulating the TH 1 arm of the immune system and protecting against hyper-immune response to an allergen. According to Dr. Sipka, the results illustrate "a striking difference between the *in vivo* immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers," (March 2009 Declaration, page 3, paragraph 6). Further, TNF-ct levels were increased significantly by 3.56 fold compared to controls for the IR-LPS, as compared with 1.66 fold for native LPS (see March 2009 Declaration, page 3, paragraph 6). Dr. Sipka specifically stated the results indicate a "surprisingly superior effect of IR-LPS over LPS in protecting against the development of hyper-immune response to an allergen neither taught nor suggested by any of the prior art" cited by the Examiner or known to him (March 2009 Declaration, page 4, paragraph 7).

Neither Khan nor Previte teach or suggest the superior effects of IR-LPS compared to native LPS in protecting against the development of allergic disease. Accordingly, Appellants submit the March 2009 Declaration provided by Dr. Sipka constitutes secondary evidence of nonobviousness rebutting any *prima facie* case of obviousness, since it clearly demonstrates that, specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results in decreasing allergic response, relative to native LPS.

For the reasons set forth above, Appellants respectfully request that the Board reverse the final rejection of claims 1-3, 5, 10, 17-18, and 22-25 as being obvious under 35 U.S.C. § 103 over Khan in view of Previte. "

It is the Examiner's position that Applicant is arguing limitations that are not present in the claims when they argue that "Applicants teach a continual exposure over a critical developmental period" and that "Applicants teach indirect exposure by application of IR-LPS to the environment." The claims are not limited to methods comprising these two limited assertions. "At least weekly administration during maturation of the mammal" is not equivalent to "continual exposure over a critical developmental period" and "to a living environment of the mammal" is not equivalent to "indirect exposure by application of IR-LPS to the environment" as defined by the specification. The claims are given their broadest reasonable interpretation, given

the definitions and disclosure in the specification and intranasal administration is encompassed by the term "to a living environment of the animal" contrary to Applicant's assertion.

It remains the Examiner's position that Khan need not teach prevention or permanent efficacious treatment for airway hyperresponsiveness in order to be used as a reference. The reference is being relied on for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma. The lack of complete prevention or treatment of hyperresponsiveness does not "teach away" from the instant invention.

Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non- irradiated LPS. One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safer and with less toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is again noted that LPS is fully toxic and is being used medically in both the Previte et al. and Khan et al. references.

Applicants assert evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. However, such evidence has not been brought forth in the instant application that is commensurate in scope with the claims, including the Declaration by Sandor Sipka filed on 03/02/2009. The results set forth in the declaration are neither surprising nor are they commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly. Applicants are encouraged to submit additional data that is commensurate in scope with the claimed invention to demonstrate surprising or unexpected results. The Examiner is not arguing that the data in the Declaration is not relevant. The Examiner argues that the data is not surprising or commensurate in scope with the claimed invention. The irradiated LPS is not surprisingly better than non-irradiated LPS, which is what Applicant would need to establish to prove that the results were unexpected. Further, the results do not demonstrate decreased development of allergic asthma in a neonatal or immature mammal by exposure with irradiation-detoxified LPS to a living environment.

It is the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. for purposes of the instant rejection what is or is not an "acceptable" degree of toxicity is not for Applicant to decide, nor is it a matter of what

standards are presently medically acceptable for humans in the United States. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Khan et al. references.

Irradiated LPS stimulates the Th1 arm of the animal's immune system in accordance with the present methods, so it would function in the same manner in the prior art. The motivation to use irradiated LPS over LPS has to do with decreased toxicity. The stimulation of the Th1 arm of the animal's immune system is inherent in using the irradiated LPS.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A

message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 24, 2010
Nora M. Rooney
Patent Examiner
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/Nora M Rooney/
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